National Institute for Health and Care Excellence

Health Technology Evaluation

Obinutuzumab with immunosuppressive therapies for treating lupus nephritis [ID6420] Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Company (Roche)	Yes, the proposed evaluation route is appropriate.	Thank you for your comments.
	Lupus UK	Yes, it is appropriate for NICE to appraise the use of obinutuzumab for treating lupus nephritis via a single technology appraisal, as proposed.	Thank you for your comments.
	UK Kidney Association	Can use as an alternative to rituximab where there is a clear allergy to rituximab? Currently limited equivalent alternatives.	Thank you. NICE will appraise obinutuzumab within the population outlined in its marketing authorisation. The benefits of obinutuzumab for people with an allergy to rituximab can be included in the submissions made to NICE and considered

Section	Stakeholder	Comments [sic]	Action
			by the committee during the appraisal.
	Otsuka Pharmaceuticals UK (comparator)	The topic and evaluation route are appropriate for referral to NICE.	Thank you for your comments
	Novartis Pharmaceuticals UK Ltd (comparator)	No comment	Noted, thank you
Wording	Company (Roche)	Yes, the wording is appropriate. However, in line with TA882[1], Roche believes the wording should consider that obinituzumab will be prescribed alongside existing immunosuppressive therapies. The scope should read: "To appraise the clinical and cost effectiveness of obinutuzumab with immunosuppressive therapies within its marketing authorisation for treating lupus nephritis" 1. NICE TA882, 2023. Voclosporin with mycophenolate mofetil for treating lupus nephritis. https://www.nice.org.uk/guidance/ta882	Thank you. This has been changed.
	Lupus UK	The current wording refers to the Population(s) as: "Adults with active lupus nephritis". However, there is no indication within the scoping for how disease activity will be measured or whether there is a threshold of disease activity level for eligibility. Treatments pathways for lupus nephritis are often based on classification of disease, as well as response to other treatments, so this will impact selection of appropriate comparators and subgroups (see further comments in those sections).	Thank you. The population which the guidance includes will be in line with the marketing authorisation. Currently the scope is left broad as this level

Section	Stakeholder	Comments [sic]	Action
			of information is not yet known.
	Otsuka Pharmaceuticals UK (comparator)	The technology section does not fully reflect the inclusion criteria of the relevant clinical trial. That is, participants were not exclusively active Class III or IV as participants co-exhibiting Class V disease in addition to either Class III or Class IV disease were also included.	Thank you. The scope has been amended.
	Novartis Pharmaceuticals UK Ltd (comparator)	No comment, wording is appropriate	Thank you for your comments.
Timing	Company (Roche)	Roche considers this appraisal to be urgent. Lupus nephritis (LN) is the most common organ-threatening manifestation of systemic lupus erythematosus (SLE) and remains a major cause of morbidity and mortality among patients with SLE. Around 50% of SLE patients will develop LN[2] within 5 years of SLE diagnosis. Up to 25% of these patients develop end stage renal disease (ESRD) despite treatment with current available therapies.[2] Publications show that <31% of patients have LN at SLE diagnosis[4]. LN is associated with 6x increased risk of mortality[3] compared to the general population. There is currently no cure for LN and, despite treatments available today, many patients progress to end stage renal disease. With current treatment options, only a minority of patients achieve a complete response within the first 1 to 2 years, and the rate of progression to ESRD has not decreased in recent decades. In addition, these standard-of-care therapies are also associated with substantial toxicities that contribute to the morbidity associated with LN. Current treatment options require patients to compromise between achieving renal response and long-term safety, leaving many patients in need of efficacious therapies. Improvements in complete renal response and a reduction in renal flares are needed to prevent irreversible	Thank you for your comments. NICE has scheduled this topic into its work programme. Equality issues identified during consultation on the draft scope are noted in the equality impact assessment form. The committee will consider these factors during the appraisal.

Section	Stakeholder	Comments [sic]	Action
		kidney damage and resulting renal morbidity. Given the seriousness of this condition, the limited efficacy of current standard of care, and the toxicities associated with current standard of care, there remains a high need for new safe and effective therapies for the treatment of proliferative LN. Obinutuzumab is a humanized type II anti-CD20 monoclonal antibody that binds to the CD20 antigen, a proven target for CD20+ B cells. Obinutuzumab offers disease-modifying treatment effects in LN including deep B-cell depletion, complete renal response and reduced renal flares with a favourable safety profile and convenient bi-annual dosing. LN imposes both direct (cost of care and associated non-medical costs) and indirect (cost of lost productivity, reduced patient quality of life) impacts on patients, caregivers, and society at large.[5] There are significant health inequities among patients with LN. There is a need for a consistent approach to the diagnosis and treatment of lupus across the UK to address various issues, including inconsistency in diagnostics, and access to treatment and how these result in inequity for people with lupus. A revised, evidence-based guideline can address these issues.[6] 2. AMIA Annu Symp Proc. 2022; 2022: 221–230.R. Saxena et al. Lupus Nephritis: Current Update. Arthritis Research & Therapy. 2011; 13:240. 3. Arthritis Rheumatol. 2023 April ; 75(4): 567–573. doi:10.1002/art.42375 - file:///Users/postinp1/Downloads/cdc_126397_DS1%20(2).pdf 4. Lupus. 2020 Aug; 29(9): 1011–1020. 5. Meacock et al, 2013: The humanistic and economic burden of systemic lupus erythematosus	

Section	Stakeholder	Comments [sic]	Action
		6. Yusof et al, 2023. Management and treatment of children, young people and adults with systemic lupus erythematosus: British Society for Rheumatology guideline scope. https://doi.org/10.1093/rap/rkad093	
	UK Kidney Association	Lack of incentive to continue manufacture by Roche. [What is the relative urgency of this evaluation to the NHS?]	Thank you for your comments. NICE has scheduled this topic into its work programme.
	Otsuka Pharmaceuticals UK (comparator)	The timing of this appraisal is appropriate	Thank you for your comments.
	Novartis Pharmaceuticals UK Ltd (comparator)	No comment	Thank you for your comments.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Company (Roche)	**Background information** The information in the background summary is largely appropriate. We note that the British Society for Rheumatology (BSR) clinical guideline for the management of SLE was published in 2017 and since then there have been rapid advances in the diagnosis, assessment, and therapeutic management of SLE, therefore warranting an update.[6] The update will incorporate these advances including non-pharmacological and pharmacological management, organ-specific treatment, as well as general holistic approaches. This will be the first guideline in SLE using a whole life course approach from childhood through adolescence and adulthood.	Thank you. The scope is intended to be a summary. Detail around the differential epidemiology and presentation of lupus nephritis in different groups of people can be

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		We believe that some additional context to the epidemiology numbers could be given, provided below: *Up to 60% of people with SLE develop lupus nephritis.* Roche believes that around 50% of SLE patients will develop LN[2] within 5 years of SLE diagnosis, and up to 25% of these patients develop ESRD despite treatment with current available therapies.[2] Compared to women, men are more likely to present with more severe LN and progress quicker. Publications show that <31% of patients have LN at SLE diagnosis[4]. *Lupus nephritis is also more prevalent in women than in men.* It is well documented that around 90% of patients with SLE are women.[7] Regarding the treatment landscape, we agree that current treatments aim to preserve renal function. Current options aim to slow progression to end stage renal disease through acute management of LN symptoms. Obinutuzumab will provide an alternative treatment option with a different mechanism of action. Obinutuzumab targets CD20-expressing B cells and promotes B cell death. B cells play a key role and serve multiple functions in the disease pathogenesis through autoantibodies, immune complexes, and amplifying activation of adaptive immune responses.[8] Compared with type I anti-CD20 antibodies, obinutuzumab has greater antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis, has more direct B-cell–killing effects, and is less reliant on complement-dependent cytotoxicity.[9] Obinutuzumab, as an efficacious therapy, offers not only effective symptom management, but also has the potential for deep B cell depletion in people with LN. **The technology** The brand name for obinutuzumab should be “Gazyvaro”.	presented within the submissions and considered by committee during the appraisal. The difference in prevalence, severity and disease progression by gender has been added to the scope and summarised in the Equalities Impact Assessment and will be considered by the committee during the appraisal. The brand name of obinutuzumab has been updated. However, the scope template has been simplified since the scope for TA882 was published and no longer includes the drug’s mechanism of action. The description focuses on phase 3 trials and is meant to be a very brief summary. But the classes of lupus

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		Roche also considers it is important to add the obinutuzumab mechanism of action, in line with TA882.[1] Suggested text below: “Obinutuzumab (Gazyvaro, Roche) is a humanized type II anti-CD20 monoclonal antibody that binds to CD20-expressing B cells and promotes B cell death. Obinutuzumab depletes autoimmune B cells. Obinutuzumab is administered intravenously every 6 months after the first year. Obinutuzumab does not currently have a marketing authorisation in the UK for adults with lupus nephritis. It has been studied in REGENCY, a Phase 3 study in people with Class III or IV lupus nephritis, with or without Class V, compared with placebo alongside standard care including mycophenolate mofetil and corticosteroids.[10] Obinutuzumab has also been investigated in NOBILITY, a Phase 2 study in people with Class III or IV lupus nephritis compared with placebo alongside standard care including mycophenolate mofetil and corticosteroids.[11] 1. NICE TA882, 2023. Voclosporin with mycophenolate mofetil for treating lupus nephritis. https://www.nice.org.uk/guidance/ta882 2. AMIA Annu Symp Proc. 2022; 2022: 221–230.R. Saxena et al. Lupus Nephritis: Current Update. Arthritis Research & Therapy. 2011; 13:240. 4. Lupus. 2020 Aug; 29(9): 1011–1020. 6. Yusof et al, 2023. Management and treatment of children, young people and adults with systemic lupus erythematosus: British Society for Rheumatology guideline scope. https://doi.org/10.1093/rap/rkad093 7. Weckerle, C. E., & Niewold, T. B. 2011) The unexplained female predominance of systemic lupus erythematosus: clues from genetic and cytokine studies. https://doi.org/10.1007/s12016-009-8192-4 8. Foster MH. T cells and B cells in lupus nephritis. Semin Nephrol 2007;27:4758. 9. Mössner et al, 2010. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. 115:4393402. 10. F. Hoffmann-La Roche Ltd, 2022. A clinical trial to look at how well obinutuzumab works in treating people with lupus nephritis and how safe it is (REGENCY) (Clinical Trial No. NCT04221477). https://clinicaltrials.gov/ct2/show/NCT04221477	nephritis included in the phase 3 trial have been amended.

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		11. Furie et al, 2022. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial; 81:100-107.	
	Genetic Alliance UK	Genetic Alliance UK spoke to one of the other stakeholders listed for this consultation, The Lupus Trust, who commented that this is a major unmet need in the treatment of lupus nephritis especially as trials in this area are notoriously difficult to conduct. It was felt that the consultation document reads well, although the section on symptoms on lupus nephritis (LN) could be rephrased to be more inclusive of symptoms seen with active SLE. Symptoms of LN include: foamy urine, oedema (in the legs, feet, ankles, hands or face), high blood pressure, joint pain or swelling, muscle pain, fever with no known cause, cutaneous lupus skin lesions and major organ disease including pulmonary, cardiovascular and neurological disease.	Thank you. The scope is intended to be a summary. More information on the impact of lupus nephritis and unmet need can be summarised in the submissions received by NICE to be considered by the committee during the appraisal.
	Kidney Research UK	Generally good, clear background section which covers many important points. We have some specific comments: • We suggest it makes clear that end-stage kidney disease is irreversible and requires lifelong dialysis or transplantation. This is not only deeply impactful on patients, but also has significant cost implications for the NHS. (The additional cost of treating lupus nephritis with Obinutuzumab therefore needs to be weighed against better sustained remission rates and reduced risk of progression to end-stage kidney disease requiring dialysis or a transplant) • Increased morbidity risk (as well as mortality risk) in patients with lupus nephritis should be highlighted. Lupus nephritis, if inadequately treated, leads to chronic kidney disease, which is associated with substantially increased morbidity, due in particular to an increased risk of cardiovascular disease. Increased morbidity has important cost	Thank you. The scope is intended to be a summary. More information on the condition and issues with current treatments can be summarised in the submissions received by NICE which will be considered by the committee during the appraisal. However, the scope has been updated to note

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		implications, in addition to the impact it has on patients' lives and function etc. • The fact that up to 60% of patients with systemic lupus erythematosus (SLE) develop lupus nephritis is already stated – worth highlighting that this makes it the most common organ-threatening manifestation of the disease • 30% of patients with lupus nephritis develop irreversible end stage kidney failure i.e. this is not a rare complication. Worth including this statistic to emphasise the risk of progression. • In the last paragraph detailing existing treatments, it needs to highlight that current treatments, even when used in combination, achieve sustained kidney remission rates in <50% of patients with lupus nephritis. This means the majority of patients with lupus nephritis remain at significant risk of developing progressive CKD, and ultimately end stage kidney disease. So there is an important unmet clinical need for better treatments. • Suggest need to highlight in the introduction that the efficacy of rituximab is limited by the extent and duration of B cell depletion which is commonly incomplete and short-lived (particularly with repeated treatment). Full B cell depletion of prolonged duration has been associated with an improved clinical response to rituximab. But most patients treated with rituximab don't achieve prolonged B cell depletion. Therefore, there is a clear rationale and unmet need for medications that can achieve more sustained B cell depletion to improve sustained remission rates in patients with lupus nephritis. We suggest changing "the use of immunosuppressive varies" in the last paragraph to "the choice of immunosuppressive agent used varies". Otherwise implies that immunosuppression isn't always used/needed	the lifelong need for dialysis or transplant, the choice of immunosuppressive agents and the risk of developing progressive chronic kidney disease and end stage kidney disease.
	Lupus UK	The background information mentions how lupus nephritis is more prevalent in those with Indo-Asian, Afro-Caribbean, and Chinese ancestry, and in	Thank you. The scope is intended to be a

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		women. However, it does not discuss important and significant differences in severity or treatment response, or the increased prevalence and severity in those diagnosed in childhood (1 in 5 cases of SLE). Additionally, although lupus nephritis is more prevalent in women than men (as the background information states), there is some evidence that men with SLE are at higher risk of lupus nephritis. We would recommend this additional information is included and should be included as part of any appraisal of treatment for lupus nephritis. Below is some reference material and summary data for your use: • SLE is more prevalent in women than men (at a ratio of approximately 9:1). However, the prevalence of lupus nephritis specifically has been found to be around 5:1. This means that, although there is higher prevalence among women, men with SLE may be at higher risk of developing lupus nephritis. (e.g. Patel et al, 2006). • Some studies have suggested that, not only is lupus nephritis more prevalent in those with particular ethnic minority ancestries, but that it is also more severe in those cases. There is mixed evidence whether this is due to epigenetic/biologic differences or factors of health inequalities (some examples below). Regardless of the cause of these findings, the fact it tends to be more severe in these groups is an important equalities issue for consideration, particularly given that patients of an ethnic minority are less likely to be included in clinical trials. o Some studies, including those in the UK, have identified comparatively accelerated organ damage accrual in those from particular ethnic minority backgrounds (e.g. Alarcón et al., 2001; Kallas et al., 2022; Segura et al., 2020). o Some genetic variants have been identified which may contribute to differential risk among those of ethnic minority backgrounds (e.g. Lanata et al, 2018; Limou et al, 2014).	summary. More information on the condition and issues with current treatments, and how experience differs in different groups, can be summarised in the submissions received by NICE which will be considered by the committee during the appraisal. The difference in prevalence, severity and disease progression by gender has been added to the scope. The issues raised have also been highlighted in the Equalities Impact Assessment and will be considered by the committee during the appraisal. With regard to juvenile-onset SLE: the scope population has been updated to people with lupus nephritis. The

Section	Consultee/ Commentator	Comments [sic]	Action
		○ However, other studies have suggested that socio-economic factors or health inequalities may be more important than ethnicity itself in driving differential risk (e.g. Parodis et al, 2023; Petri et al, 2021; Segura et al., 2020) • Alongside differential risk of different ethnic ancestries, some research suggests that ethnicity may impact treatment response, including both treatment outcome and adverse effects (e.g. Isenberg et al., 2010; Merrill et al., 2010; Dooley et al, 1997). • SLE develops in childhood (Juvenile-onset SLE; JSLE) in approximately 20% of cases. Lupus nephritis is more likely in JSLE, occurring in 50% of cases, with only 40–60% of patients achieving complete remission (Oni et al, 2021). This same study suggests the rate of chronic kidney disease (CKD) 5 is up to 15% and the presence of lupus nephritis has an established link with an associated increase in mortality in people with JSLE. As lupus does not have a cure, this means that adults with SLE whose disease began in childhood (JSLE) are more likely to experience lupus nephritis. This is particularly important to note as there is variability in treatment and few treatments approved for JSLE and lupus nephritis in children specifically. References • Alarcón, G.S., McGwin Jr, G., Bartolucci, A.A., Roseman, J., Lisse, J., Fessler, B.J., Bastian, H.M., Friedman, A.W. and Reveille, J.D., 2001. Systemic lupus erythematosus in three ethnic groups: IX. Differences in damage accrual. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, *44*(12), pp.2797-2806. • Dooley, M.A., Hogan, S., Jennette, C. and Falk, R., 1997. Cyclophosphamide therapy for lupus nephritis: poor renal survival in black Americans. *Kidney international*, *51*(4), pp.1188-1195. • Isenberg, D., Appel, G.B., Contreras, G., Dooley, M.A., Ginzler, E.M., Jayne, D., Sanchez-Guerrero, J., Wofsy, D., Yu, X. and Solomons, N., 2010. Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study. *Rheumatology*, *49*(1), pp.128-140.	REGENCY clinical trial (obinutuzumab compared with placebo in people with lupus nephritis) was restricted to people over 18 years old. Another trial studying obinutuzumab in people with lupus nephritis included people 14 years old and above. The appraisal will appraise the clinical and cost effectiveness of the treatment within its marketing authorisation, which has not been granted at this time.

Section	Consultee/ Commentator	Comments [sic]	Action
		• Kallas, R., Li, J., Goldman, D.W., Magder, L.S. and Petri, M., 2022. Trajectory of damage accrual in systemic lupus erythematosus based on ethnicity and socioeconomic factors. *The Journal of Rheumatology*, *49*(11), pp.1229-1235. • Lanata, C.M., Nititham, J., Taylor, K.E., Chung, S.A., Torgerson, D.G., Seldin, M.F., Pons-Estel, B.A., Tusié-Luna, T., Tsao, B.P., Morand, E.F. and Alarcón-Riquelme, M.E., 2018. Genetic contributions to lupus nephritis in a multi-ethnic cohort of systemic lupus erythematous patients. *PloS one*, *13*(6), p.e0199003. • Limou, S., Nelson, G.W., Kopp, J.B. and Winkler, C.A., 2014. APOL1 kidney risk alleles: population genetics and disease associations. *Advances in chronic kidney disease*, *21*(5), pp.426-433. • Merrill, J.T., Neuwelt, C.M., Wallace, D.J., Shanahan, J.C., Latinis, K.M., Oates, J.C., Utset, T.O., Gordon, C., Isenberg, D.A., Hsieh, H.J. and Zhang, D., 2010. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, *62*(1), pp.222-233. • Oni, L., Wright, R.D., Marks, S., Beresford, M.W. and Tullus, K., 2021. Kidney outcomes for children with lupus nephritis. *Pediatric Nephrology*, *36*, pp.1377-1385. • Petri, M., Purvey, S., Fang, H. and Magder, L.S., 2012. Predictors of organ damage in systemic lupus erythematosus: the Hopkins Lupus Cohort. *Arthritis & Rheumatism*, *64*(12), pp.4021-4028. • Parodis, I., Lanata, C., Nikolopoulos, D., Blazer, A. and Yazdany, J., 2023. Reframing health disparities in SLE: A critical reassessment of racial and ethnic differences in lupus disease outcomes. *Best Practice & Research Clinical Rheumatology*, p.101894. • Patel, M., Clarke, A.M., Bruce, I.N. and Symmons, D.P., 2006. The prevalence and incidence of biopsy-proven lupus nephritis in the UK: evidence of an ethnic gradient. *Arthritis & rheumatism*, *54*(9), pp.2963-2969. • Segura, B.T., Bernstein, B.S., McDonnell, T., Wincup, C., M Ripoll, V., Giles, I., Isenberg, D. and Rahman, A., 2020. Damage accrual and mortality over long-term follow-up in 300 patients with systemic lupus erythematosus in a multi-ethnic British cohort. *Rheumatology*, *59*(3), pp.524-533.	
	Otsuka Pharmaceuticals UK (comparator)	No changes suggested.	Noted, thank you

Section	Consultee/ Commentator	Comments [sic]	Action
	Novartis Pharmaceuticals UK Ltd (comparator)	No comment	Noted, thank you
Population	Company (Roche)	No comments.	Noted, thank you
	Kidney Research UK	Yes [appropriate]	Noted, thank you
	UK Kidney Association	Yes [appropriate]	Noted, thank you
	Lupus UK	The current wording refers to the Population(s) as: “Adults with active lupus nephritis”. However, there is no indication within the scoping for how disease activity will be measured or whether there is a threshold of disease activity level for eligibility. Treatments pathways for lupus nephritis are often based on classification of disease, as well as response to other treatments, so this will impact selection of appropriate comparators and subgroups (see further comments in those sections).	Thank you. The population which the guidance includes will be in line with the marketing authorisation. Currently the scope is left broad as this level of information is not yet known.
	Otsuka Pharmaceuticals UK (comparator)	In line with the relevant clinical trial inclusion criteria, the population in scope should be active lupus nephritis.	Thank you. The population which the guidance includes will be in line with the marketing authorisation. Currently the scope is left broad as this level

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			of information is not yet known.
	Novartis Pharmaceuticals UK Ltd (comparator)	As Lupus nephritis is divided into classes (I to VI) we suggest that the scope specify that the LN population considered in this assessment is limited to classes 3 or 4.	Thank you. The guidance will be in line with the marketing authorisation. Currently the scope is left broad as this level of information is not yet known.
Subgroups	Company (Roche)	There are no subgroups within this population that should be considered separately. Obinutuzumab is an effective treatment across all subgroups. A broad population ensures the value of obinutuzumab is assessed to reduce unmet need for the greatest number of patients and address health inequalities across the system.	Thank you for your comments
	Kidney Research UK	Need to consider that ethnic minority groups tend to respond less well to existing treatments and therefore have poorer outcomes with higher rates of progression to end stage kidney disease. >50% of patients included in the positive phase II nobility trial of Obinutuzumab, were from ethnic minority groups demonstrating that Obinutuzumab is effective in improving treatment outcomes in these harder to treat patient groups. Patients from ethnic minority groups therefore stand to gain particular benefit from the approval of Obinutuzumab for treating lupus nephritis. Patients who demonstrate poor adherence with oral therapy should be considered separately as these patients have poorer clinical outcomes (vs.	Thank you. Your comments have been noted. It has been noted in the Equalities Impact Assessment form that people of different ethnicities respond differently to existing treatments, and that that obinutuzumab may

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		adherent patients) and stand to gain particular benefit from Obinutuzumab as a directly observed intravenous therapy.	be effective in improving treatment outcomes for people from ethnic minority backgrounds. The committee will consider these factors during the appraisal. Although the scope has not specified potential subgroups (i.e. adherence to oral therapy) the appraisal committee can consider whether there are subgroups for whom the effectiveness evidence suggests differential cost effectiveness. However, final guidance will be issued in accordance with the marketing authorisation.
	Lupus UK	The appraisal may need to consider different classes of lupus nephritis as specific subgroups, whether the appraisal is intended for all classes of lupus nephritis or for specific ranges. Existing treatment pathways vary based on the presenting class of lupus nephritis (e.g. patients must be class V to have calcineurin inhibitors or rituximab recommended). Class of disease will impact appropriate treatment comparators, and also potential cost-benefit analysis if	Thank you. Although the scope has not specified potential subgroups (i.e. classification of lupus) the appraisal committee

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		obinutuzumab is effective at reducing damage and preventing progression of disease (and so preventing the need for other treatments only available to those with class V kidney disease or kidney failure). The appraisal may also need to consider ethnicity, where research is available, given the potential differences in treatment response (as described in the background section of our response). This should be considered in two ways: 1) whether obinutuzumab is more effective in people with particular ethnic ancestry; and 2) whether the appropriate comparator treatment may need to be different according to patient ethnicity (for example different levels of effectiveness of rituximab associated with ethnicity in the studies cited in the background section of our response).	can consider whether there are subgroups for whom the effectiveness evidence suggests differential cost effectiveness. However, final guidance will be issued in accordance with the marketing authorisation. It has been noted in the Equalities Impact Assessment form that people of different ethnicities respond differently to existing treatments, and that that obinutuzumab may be more effective for people of different ethnicities. The committee will consider these factors during the appraisal.
	UK Kidney Association	Patients with a documented allergy to rituximab. Obinutuzumab is an excellent alternative.	Thank you. Although the scope has not specified potential subgroups (i.e. people with an allergy to rituximab) the appraisal

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			committee can consider whether there are subgroups for whom the effectiveness evidence suggests differential cost effectiveness. However, final guidance will be issued in accordance with the marketing authorisation.
	Otsuka Pharmaceuticals UK (comparator)	In the relevant clinical trial, Participants with an adequate response at Week 76 continued in the study. Response based analysis should be considered in the appraisal.	Thank you. The appropriateness of alternative methods of analysis can be considered and then presented by the company in its submission, for consideration by the committee during the appraisal. No changes to the draft scope required.
	Novartis Pharmaceuticals UK Ltd (comparator)	No comment	Thank you for your comments. No action needed.

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Comparators	Company (Roche)	Roche agrees that the comparators included in the draft scope are all used in the UK for the treatment of LN. However, it is important to note that not all are licensed, or would be considered standard of care for LN. Several of the comparators listed in the draft scope do not currently have a marketing authorisation in the UK for this indication, including mycophenolate, azathioprine and rituximab. This information should be included for clarity.	Thank you for your comments. The appraisal committee can consider comparator technologies that do not have a marketing authorisation for the indication defined in the scope when they are considered to be part of established clinical practice for the indication in the NHS.
	Kidney Research UK	Azathioprine is not a recommended agent for treatment induction (maintenance only) – we suggest removing it from the list of induction treatments. Suggest change order of induction agents so mycophenolate and cyclophosphamide are at the top as these are the most frequently used induction agents.	Azathioprine has been removed from the scope as an induction agent. The comparators have been listed alphabetically rather than by frequency of use.
	Lupus UK	The comparators listed within the Draft Scope are currently used in the NHS for the treatment of lupus nephritis. However, it is important to note that, as a heterogenous disease, there is no single 'best' treatment, treatment response can vary considerably between patients, and some cases are refractory to all available treatments. This means it is not possible to describe any of the currently available treatments	Thank you for your comments. The most appropriate comparators can be discussed in more detail in the submissions

Section	Consultee/ Commentator	Comments [sic]	Action
		as 'best alternative care' for all patients as there is no regimen that is effective for all. It also means that, even where there are treatments which have been shown to be effective and have been approved, there is a need for more treatments, particularly for those patients who are refractory. Relatedly, there is considerable variation in access to these therapies. A recent UK-based study suggested that there is geographical variation in treatment protocols and access to specialist management (Ibrahim et al., 2024). This means not all patients will have access to suggested comparators. Appropriate comparators may also be impacted by whether this appraisal is considering obinutuzumab across all classes of lupus nephritis or a defined range, as most treatments pathways and protocols relate to specific ranges of disease activity and response to other treatments. It is worth noting that rituximab is currently not licensed for the treatment of SLE but is available as a treatment option through routine commissioning for refractory SLE in adults and post-pubescent children. It can only be used where the patient has failed to respond, or has had adverse events, to two or more immunosuppressive therapies, has particular disease activity scores, is managed by a specialist centre, and is not eligible for clinical trials or belimumab. <u>References:</u> Ibrahim, S.T., Edwards, C.J., Ehrenstein, M.R., Griffiths, B., Gordon, C., Hewins, P., Jayne, D., Lightstone, L., McLaren, Z., Rhodes, B. and Vital, E.M., 2024. Differences in management approaches for lupus nephritis within the UK. *Rheumatology Advances in Practice*, *8*(1), p.rkae017.	made to NICE, to be considered by the committee during the appraisal. The appraisal committee can consider comparator technologies that do not have a marketing authorisation for the indication defined in the scope when they are considered to be part of established clinical practice for the indication in the NHS.

Section	Consultee/ Commentator	Comments [sic]	Action
	UK Kidney Association	Yes	Thank you for your comments.
	Otsuka Pharmaceuticals UK (comparator)	No changes suggested	Noted, thank you.
	Novartis Pharmaceuticals UK Ltd (comparator)	In line with the recommendations of TA882 and the products SPC the scope should make clear that Voclosporin with mycophenolate mofetil rather than Voclosporin alone is a comparator In line with TA882 which recommends the use of Voclosporin in line with it marketing authorisation, Voclosporin should also be listed as a maintenance treatment in LN	Thank you for your comments. This has been updated in the scope.
Outcomes	Company (Roche)	The outcomes listed are appropriate and capture important clinical and health-related impacts of LN. However, Roche feels the scope could go further in considering some key clinical outcomes important for the prevention of end-stage renal disease, including proteinuria, the prevention of renal flares and the effects of steroid sparing. Roche also feels that the scope is too narrow to holistically consider the impact to patients, their families and the health system. Roche calls for the committee to consider a wider perspective. Chronic kidney disease is predicted to become the 5th leading cause of death globally by 2040. The NHS spends an estimated £6.4 billion per year on dialysis, which is 3.2% of the NHS budget, and is projected to spend even more on dialysis in the future, potentially rising to £10.9 billion by 2033.[12] Obinutuzumab has the potential for greater adherence to treatment which would increase the	Thank you for your comments. The list of outcomes in the scope is not intended to be exhaustive. Additional outcomes can be included in the submissions made to NICE and considered by the committee during the appraisal. However, please note, the reference case within NICE's Health technology Evaluation

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		possibility of reducing emergency care for acute symptoms as well as prevent longer-term high-cost treatment associated with ESRD (i.e. dialysis and transplant). Given the pressure on healthcare services, it is important to include outcomes relating to not only cost but also capacity savings to the NHS. Additionally, as LN predominantly affects people of working age, Roche believes ID6420 could be a candidate for NICE to consider trialling a wider societal perspective. With recent calls from the Department of Health and Social Care relating to the importance of reducing burden on the NHS and getting people back to work, it is becoming increasingly important to consider not only health impacts but also any impact to society, including lost productivity associated with having a chronic condition such as LN. 12. Kidney Research UK, 2023. Kidney disease: A UK public health emergency - The health economics of kidney disease to 2033; https://www.kidneyresearchuk.org/wp-content/uploads/2023/06/Economics-of-Kidney-Disease-full-report_accessible.pdf	Manual (section 4.2) specifies that health effects 'for patients or, when relevant, carers' can be considered for the perspective on outcomes. It also specifies an NHS and personal social service perspective for costs. Any choices outside the reference case can be considered by committee, but must be clearly specified and justified (see section 4.2.3).
	Kidney Research UK	The outcomes listed are appropriate Need to add proteinuria reduction as a specific outcome measure to be considered. There is good evidence that reduction in proteinuria to 0.7g per day by 12 months is the most useful predictor of preserved kidney function at 7 years (MAINTAIN nephritis trial, 2015, Lupus Sci Med). This is important as we don't currently have long-term follow-up data on use of Obinutuzumab, so we are currently unable to determine the effectiveness of Obinutuzumab in reducing the incidence of end stage renal disease, an important outcome measure. Reduction in proteinuria is a useful outcome measure that can be used at earlier timepoint as a surrogate to predict longer term outcomes on the incidence of end stage kidney disease.	Thank you. The list of outcomes in the scope is not intended to be exhaustive. Additional outcomes can be included in the submissions made to NICE and considered by the committee during the appraisal.

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	Lupus UK	An outcome measure not currently included is “access to treatment”. As noted in the above response, some treatments, such as rituximab, can only be administered by, or under shared care with, a specialist centre, which can have significant geographical and financial barriers, resulting in those from poorer socio-economic groups being unable to accept the treatment if offered. If obinutuzumab does not require the same level of specialist centre support, it may not present the same barriers. The appraisal should also consider morbidity secondary to lupus nephritis as outcome measures, as people with lupus nephritis have a higher incidence of secondary complications such as cardiovascular events and infections. For example, a recent meta-analysis showed lupus nephritis was significantly associated with increased risk of cardiovascular disease risk factors compared to those with SLE without nephritis (Wong et al., 2024). “Health-related quality of life” (HRQoL) is listed as an outcome measure. It is important that this is measured appropriately for a fair comparison of outcome measures to be made. For example, some commonly used HRQoL measures may have differing sensitivity to change in SLE patients (Mikdashi, 2018). “Health-related quality of life” should also consider qualitative research and outcomes reported to be important to patients as part of the wider appraisal. For example, fatigue is often reported as the most burdensome symptom of lupus nephritis (and SLE more widely),but is not fully captured in standard HRQoL measures. “Adverse effects of treatment” is listed as an outcome measure, which we would expect to include rates of infection due to immunosuppressive qualities of treatments. We believe that this should be expanded to include reports of vaccine-preventable infections. For example, findings from studies examining efficacy of COVID-19 vaccination in immunosuppressed groups have	Thank you. The outcome measures in the scope describe the principal health outcome measures appropriate for the analysis; access to treatment is not a health outcome measure and so it not relevant. However, difficulties accessing treatment, particularly for people from different socioeconomic, can be outlined in the submissions made to NICE and considered by the committee during the appraisal. This has also been captured in the Equalities Impact Assessment. The EQ-5D is the preferred measure of health-related quality of life. If an alternative measure is used evidence must be provided that shows why EQ-5D is not

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		indicated that rituximab and cyclophosphamide may be attributed with lower vaccine efficacy. As an immune-suppressing therapy, we would expect obinutuzumab to potentially reduce the protection offered by vaccination. However, the degree to which it does this is important. If patients taking obinutuzumab have reasonable vaccine responses, it should be considered favourably for this patient group – especially due to kidney disease being recognised as a significant risk factor for serious disease from infections such as COVID-19 and seasonal influenza. All proposed outcomes should ensure they are appropriate to the class (or range of classes) of lupus nephritis obinutuzumab and any comparators are being used for. For example, patients with class IV disease may experience significantly higher morbidity or mortality, and have lower HRQoL scores, then those with class I lupus nephritis (e.g. Kharawala et al, 2022, on HRQoL). <u>References</u> • Kharawala, S., Kaur, G., Shukla, H., Scott, D.A., Hawkins, N., Chen, W.H. and Gairy, K., 2022. Health-related quality of life, fatigue and health utilities in lupus nephritis: A systematic literature review. *Lupus*, *31*(9), pp.1029-1044. • Mikdashi, J., 2018. Measuring and monitoring health-related quality of life responsiveness in systemic lupus erythematosus patients: current perspectives. *Patient Related Outcome Measures*, pp.339-343. • Wong, C.Y., Ma, B.M., Zhang, D., Cheung, W., Chan, T.M. and Yap, D.Y., 2024. Cardiovascular risk factors and complications in patients with systemic lupus erythematosus with and without nephritis: a systematic review and meta-analysis. *Lupus Science & Medicine*, *11*(1), p.e001152.	appropriate. A detailed account of how the alternative measure was generated, its validity and how it affects utility values should also be provided. No action needed. The list of outcomes in the scope is not intended to be exhaustive. Additional outcomes can be included in the submissions made to NICE and considered by the committee during the appraisal.
	UK Kidney Association	Cumulative cyclophosphamide exposure. Time to b-cell repletion. Double stranded DNA levels.	Thank you for your comment. The list of outcomes in the scope is not intended to be

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			exhaustive. Additional outcomes can be included in the submissions made to NICE and considered by the committee during the appraisal.
	Otsuka Pharmaceuticals UK (comparator)	The outcomes in the final scope should also include proteinuria reduction. Evidence suggests proteinuria at 12 months of LN treatment is the single best predictor of long-term outcome. Reference: Dall'Era M, Cisternas MG, Smilek DE, Straub L, Houssiau FA, Cervera R, Rovin BH, Mackay M. Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-Lupus Nephritis cohort. Arthritis Rheumatol. 2015 May;67(5):1305-13. doi: 10.1002/art.39026. PMID: 25605554.	Thank you. The list of outcomes in the scope is not intended to be exhaustive. Additional outcomes can be included in the submissions made to NICE and considered by the committee during the appraisal. No action needed.
	Novartis Pharmaceuticals UK Ltd (comparator)	Outcomes are appropriate and in line with TA882	Thank you for your comments.
Equality	Company (Roche)	More than 7.2 million are living with kidney disease in the UK, including LN, where many of whom will be undiagnosed and unaware that they are in the early stages of disease.[12, 13] However, kidney disease impacts some communities much more than others. The recently published ACR guidelines from December 2024 stated that "Healthcare disparities impact outcomes in people with LN; implementation of	Thank you for your comments. These factors have been noted in the Equalities Impact Assessment form and will be considered by

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		treatment recommendations is aimed to alleviate health disparities". For example, South Asian adults develop kidney disease younger than white adults[13,14] and people from low socioeconomic groups are more likely to develop chronic kidney disease than those in higher socioeconomic groups.[15] Kidney disease progresses faster in some people. For example, people of Black, Asian or mixed heritage are more likely to experience kidney failure than people of white heritage[16], under-70s living in deprivation are more than twice as likely to progress to kidney failure than those in more affluent areas[17], more men than women start treatment for kidney failure[17], and mental health conditions are associated with faster disease progression and worse outcomes for people with kidney disease.[18] Finally, not everyone receives the same quality of care or focus in research. For example, the largest gap in early diagnosis is among Black, Asian and other minority populations[12], and women, people from Black heritage communities and people living in the most deprived areas are less likely to get tests and treatments for kidney disease.[19] There is a need for a consistent approach to the diagnosis and treatment of SLE across the UK to address various issues including inconsistency in diagnostics and access to treatment and how these result in inequity for people with SLE.[6] Wider health inequalities have been recognised in various policies and guidelines, and some innovations brought about by the Covid-19 pandemic provided a blueprint for equity-led approaches. However, due in part to the challenging economic and health service environment, this hasn't yet translated into closing the unfair gaps in kidney health, access to care and progression of disease. 6. Yusof et al, 2023. Management and treatment of children, young people and adults with systemic lupus erythematosus: British Society for Rheumatology guideline scope. https://doi.org/10.1093/rap/rkad093	the committee during the appraisal.

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		12. Kidney Research UK, 2023. Kidney disease: A UK public health emergency - The health economics of kidney disease to 2033. https://www.kidneyresearchuk.org/wp-content/uploads/2023/06/Economics-of-Kidney-Disease-full-report_accessible.pdf 13. Kidney Research UK, 2024. Time To Act: A New Review of Kidney Health Inequalities. https://www.kidneyresearchuk.org/wp-content/uploads/2024/07/FINAL-Accessible-lay-Report-_Academic_Report-Lay-Summary_V11-07.pdf 14. Major et al. Comorbidities and outcomes in South Asian individuals with chronic kidney disease: An observational primary care cohort. 15. So et al. Socio-economic status influences chronic kidney disease prevalence in primary care: a community-based crosssectional analysis 16 UK Kidney Association. Ethnicity disparities in patients with kidney failure in England and Wales. 2023. 17 UK Kidney Association. Social and economic disparities in patients with kidney failure in England and Wales. 2023. 18 Kidney Research UK. Addressing the mental health challenges of life with kidney disease. The case for change. 2023 19 Phillips, K., et al. Inequalities in the management of diabetic kidney disease in UK primary care: A cross-sectional analysis of a large primary care database.	
	Kidney Research UK	We don't think any changes in this regard are required.	Noted, thank you
	Lupus UK	As mentioned in our comments under 'Background Information' lupus nephritis affects people of all ethnic groups but is more prevalent, and has poorer outcomes in, people of African, Caribbean, and Chinese heritage. People of Black African/Caribbean heritage are also at a higher risk of developing diabetes and hypertension. It should be considered whether steroid-sparing treatments such as obinutuzumab could have additional advantages over standard treatments by reducing some adverse effects and risks of comorbidities – especially considering the high dependence on corticosteroids in current standard therapy. Relatedly, as discussed further in our response to the 'background information' section, there may be differences in treatment response related to ethnicity. Alongside the wider issues of nephritis as a heterogeneous	Thank you for your comments. The factors have been highlighted in the Equalities Impact Assessment and will be considered by the committee during the appraisal.

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		disease requiring a range of treatment options, the appraisal should consider whether a greater range of available treatments may particularly benefit those from minority ethnic backgrounds who are more likely to develop lupus nephritis, more likely to have an accelerated progression of disease, and are likely to be impacted by the variation in treatment due to health inequalities.	
	UK Kidney Association	Access for patients allergic to rituximab.	Thank you for your comment. The submissions from the company, patient and professional organisations should include concerns and considerations about access for patients allergic to rituximab.
	Otsuka Pharmaceuticals UK (comparator)	No equality issues identified.	Noted, thank you
	Novartis Pharmaceuticals UK Ltd (comparator)	No comment	Noted, thank you
Other considerations	Company (Roche)	No comments.	Noted, thank you
	Kidney Research UK	Suggest that the economic analysis assesses the cost effectiveness of Obinutuzumab, not just by determining the incremental cost per quality adjusted life year, but also specifically by the predicted cost savings	Thank you for your comments. NICE's Health technology

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		associated with reduction in disease flares. Disease flares require either an increased frequency of outpatient clinic appointments, or not uncommonly an inpatient admission for a period of days/weeks to facilitate urgent investigation and treatment, which can include kidney biopsy, intravenous administration of corticosteroid, cyclophosphamide or diuretic therapy, and occasionally a need for acute dialysis. This increased contact with clinical services and potential requirement for emergency care has a significant cost implication and this needs to be weighed carefully against the cost of Obinutuzumab which typically requires 6-monthly infusions of 2x 1g doses for 1 year to achieve a sustained period of B cell depletion and increasing clinical benefit during the first two years after treatment.	Evaluation Manual (section 4.2.15) specifies that QALYs are the most appropriate generic measure of health benefit that reflects both mortality and health-related quality-of-life effects. If the assumptions that underlie the QALY are inappropriate in a particular case, then evidence of this should be produced. Analyses using alternative measures may be presented as an additional non-reference-case analysis.
	Otsuka Pharmaceuticals UK (comparator)	The service impact of hospital resources as a result of IV administration should be considered in the appraisal.	Comment noted. The committee will consider all relevant evidence submitted. No changes to the draft scope required.

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Questions for consultation	Company (Roche)	**Where do you consider obinutuzumab will fit into the existing care pathway for lupus nephritis? Would you expect it to be used as maintenance, as well as induction?** Obinutuzumab will fit into the existing care pathway. Obinutuzumab is administered intravenously every 6 months after the first year. Nephrology services already administer treatments intravenously, so there are no additional considerations for prescribing obinutuzumab over alternatives. Other treatments for SLE and LN are administered much more frequently. For example, belimumab for SLE is administered every 3 weeks and voclosporin for LN is administered twice daily. Obinutuzumab has the potential to reduce the system, clinical and societal burden, through twice yearly (after the first year) administration, thus improving adherence issues and reducing the need for multiple clinical appointments and frequent follow-ups. Roche expects obinutuzumab to be an additional treatment option for people with LN alongside MMF and corticosteroids. Obinutuzumab should be used as an alternative to treatments in combination with MMF (i.e. azathioprine, calcineurin inhibitors, cyclophosphamide or rituximab) or maintenance treatment with MMF alone. **Is voclosporin with mycophenolate mofetil currently used for induction or maintenance treatment?** Roche understands that voclosporin with mycophenolate mofetil is used for both induction and maintenance amongst rheumatologists. However, we understand that the use of voclosporin is variable with nephrologists, where other treatments are often preferred. **Please select from the following, will obinutuzumab be:** **A. Prescribed in primary care with routine follow-up in primary care**	Thank you for your comments. The evidence submissions can expand on the placement of obinutuzumab within the current treatment pathway and health-related benefits unlikely to be included in the QALY calculation, which will be taken into account by the appraisal committee.

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		B. Prescribed in secondary care with routine follow-up in primary care **C. Prescribed in secondary care with routine follow-up in secondary care** **D. Other (please give details):** Roche expects that obinutuzumab will be prescribed, administered and routinely followed up in secondary care. Obinutuzumab will be administered in the current care pathway, intravenously in an outpatient hospital setting. Obinutuzumab is already prescribed and administered in secondary care for chronic lymphocytic leukemia. Hospital pharmacists already stock, prepare and store obinutuzumab in this setting and we see no additional impact on the service for obinutuzumab for LN. For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. **Would obinutuzumab be a candidate for managed access?** As there is limited further data collection planned beyond the existing protocol for the REGENCY study and there are no additional studies planned for obinutuzumab specifically for the treatment of LN, Roche considers it to be unlikely that obinutuzumab would be a candidate for managed access. However, Roche remains open to all routes to patient access. **Do you consider that the use of obinutuzumab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?**	

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		Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. Yes, Roche believes that the benefits of obinutuzumab are likely to extend beyond the domains considered within the QALY calculation: - Obinutuzumab has the potential to relieve reliance on steroid treatments, which can be associated with substantial impacts to patient quality of life. Chronic corticosteroid use is associated with the accrual of irreversible organ damage over time.[20] Most of the organ damage seen in patients with LN is caused by the steroids used to treat the disease. This underlines the need for new steroid-sparing therapies to minimize organ damage.[21] It is important to capture the positive effects of steroid sparing on patient quality of life. - LN is typically diagnosed and treatment is initiated at working age. The impact of LN can result in many patients regularly missing days of work, or stopping work altogether.[22] This can have detrimental impacts on patient quality of life. Similarly, carers of patients with LN have reported the need to take time off work to provide care. This has negative impacts on their financial status and social activity, which in turn impacts carer quality of life.[23] Obinutuzumab will be administered twice yearly (after the first year), substantially reducing the administration burden experienced with current treatments. This administration regimen, not only reduces the need for multiple clinical appointments and frequent follow-ups, but has the potential to improve adherence and clinical outcomes. Both of which improve the chances of patients maintaining the freedom to work, reducing negative impacts to patient and carer quality of life. - Many patients with LN are women of childbearing age. Pregnancy associated with LN is often a cause for concern among patients, as	

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		active LN is associated with poor maternal and foetal outcomes.[24] Uncertainty over childbearing is likely to have a substantial impact on the quality of life of women with LN. - As noted in the equality section, obinutuzumab has the potential to contribute to addressing a number of health inequalities that exist in kidney disease care. These impacts to inequalities will not be captured in a standard QALY calculation. **Please indicate if any of the treatments in the scope are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics.** **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** - **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which obinutuzumab will be licensed;** - **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;**	

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		- **could have any adverse impact on people with a particular disability or disabilities.** **Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.** See response to Equality section. 20. Al Sawah et al., 2015. Effect of corticosteroid use by dose on the risk of developing organ damage over time in systemic lupus erythematosus-the Hopkins Lupus Cohort. 21. Joo et al., 2017. Lupus nephritis is associated with more corticosteroid-associated organ damage but less corticosteroid non-associated organ damage. 22. Aghdassi et al, 2011. Healthcare cost and loss of productivity in a Canadian population of patients with and without lupus nephritis. 23. Kent et al., 2017. Burden of illness in systemic lupus erythematosus: results from a UK patient and carer online survey. 24. Lightstone and A Hladunewich. 2017. Lupus Nephritis and Pregnancy: Concerns and Management.	
	Kidney Research UK	Obinutuzumab would be an important addition to current treatment options for lupus nephritis to improve remission rates beyond those achieved with standard therapies approved by NICE. There is an important unmet need to improve sustained remission rates (currently achieved in <50% of patients despite combination therapy) to reduce the risk of irreversible kidney damage that leads to progressive CKD and end-stage kidney disease. Strong clinical trial data support effectiveness of Obinutuzumab in treating lupus nephritis. Relevant data from studies examining the efficacy of rituximab in lupus nephritis show that remission rates are better in patients who achieve complete and sustained B cell depletion. Obinutuzumab therefore offers an important advantage over rituximab in delivering high rates of complete and sustained B cell depletion. We would expect it to be used as part of disease induction, and as a useful adjunctive therapy in maintaining disease remission, particularly in patients who show poor adherence to oral therapies	Thank you for your comments. Unmet need, current treatments, expected treatment settings, and health related benefits unlikely to be included in the QALY calculation can be further outlined in the submissions made to NICE and considered by the committee during the appraisal.

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		for whom treatment options with favourable side effect profiles are currently limited. Voclosporin with mycophenolate is currently used for induction treatment in patients with lupus nephritis, but can also be helpful as maintenance therapy, particularly in patients who struggle to tolerate higher doses of mycophenolate due to gastrointestinal side effects or leukopenia. Concurrent use of a calcineurin inhibitor with mycophenolate can permit a dose reduction in mycophenolate to reduce side effects whilst effectively maintaining disease remission. The additional of voclosporin to mycophenolate is also useful in treating patients with persistent heavy proteinuria after treatment induction, despite maintenance treatment with mycophenolate alone. Obinutuzumab would be prescribed in secondary care with routine follow-up in secondary care (option C). The setting for prescribing and routine follow-up does not differ for most of the comparators and subsequent treatments listed, with the possible exception of azathioprine which is prescribed in primary care by some GPs. All patients with lupus nephritis on immunosuppression should receive routine follow-up in secondary care, with secondary care services providing the appropriate blood test monitoring. Most GP practices will not prescribe mycophenolate or calcineurin inhibitors used as maintenance therapy. Rituximab and cyclophosphamide would never be prescribed outside of a secondary care setting. Obinutuzumab would be a candidate for managed access. There is strong evidence to support its effectiveness in treating lupus nephritis. It is currently used by lupus specialists in the UK to treat lupus nephritis off-label and it has an established safety record. Managed access to Obinutuzumab would offer	

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		significant benefit to patients who fail to achieve disease remission with standard therapy, improving their chances of obtaining sustained renal remission to protect them from permanent kidney damage that can lead to future progressive CKD and end-stage kidney disease. Providing faster access to Obinutuzumab for this vulnerable patient group (for whom there are currently no other NHS funded options to treat their refractory disease) to prevent these adverse outcomes would be of significant benefit. As it will take time to demonstrate the efficacy of Obinutuzumab in improving important longer term kidney outcomes such as the risk of progressive CKD or end-stage kidney disease, it is important that access to this effective treatment is not delayed whilst these longer-term outcome data are collected and analysed. Obinutuzumab is likely to result in some substantial health related benefits that are unlikely to be included in the QALY calculation. Unlike other manifestations of SLE, lupus nephritis, although a serious and organ-threatening manifestation, is often not symptomatic in its early stages, detected instead through routine monitoring of proteinuria and kidney function on blood tests. Early and important health-related benefits of successful treatment of lupus nephritis include reduction in proteinuria and stabilisation of kidney function – but this is unlikely to reflected in a QALY calculation in the short term. Reduced rates of progression to end stage kidney disease would likely only be reflected in a QALY calculation in the longer term. An additional health-related benefit of Obinutuzumab that would not necessarily be included in a QALY calculation is reduction in steroid dose/more rapid steroid withdrawal. Steroid reduction does not always result in a short-term symptomatic benefit for the patient that would be reflected in an improved quality of life score. However, it has important benefits in reducing the risk of diabetes, osteoporosis and infection (which would all have longer-term health, quality of life and economic benefits)	

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		There is good evidence that reduction in proteinuria to 0.7g per day by 12 months is the most useful predictor of preserved kidney function at 7 years (MAINTAIN nephritis trial, 2015, Lupus Sci Med). The effective reduction in proteinuria achieved by Obinutuzumab treatment (demonstrated in both the nobility and regency trials) should be considered as a substantial health-related benefit that may not be included in a QALY calculation.	
	Lupus UK	1. Question re managed access: Yes, obinutuzumab should be considered for managed access if there is insufficient evidence to approve it for use during this appraisal. It could also be considered for managed access for children and/or adolescents, if more evidence is required for this age group as they are more likely to develop lupus nephritis (and this appraisal is only considering adults with lupus nephritis). It should also not only be appraised on the basis of cost-effectiveness related to comparator treatments. As a heterogenous disease with varied treatment responses, there is an unmet need for patients who are refractory to other available treatments. If obinutuzumab was found to be effective, but not more cost effective than comparators, it should still be made available on the NHS, at the very least, for those patients with no feasible treatment options. 2. Question re other health-related benefits unlikely to be captured in QALY calculation: Alongside the points in our response in the “outcomes” section about considering secondary morbidities such as cardiovascular disease and considering PROMs such as fatigue which may not be fully captured in HRQoL measures, the appraisal should consider whether the calculation sufficiently accounts for the potential benefits of reducing or preventing the further accumulation of damage, particularly for those who are refractory to other treatments or who are more likely to have an accelerated course of damage. This may include benefits of preventing the need for treatment for	Unmet need including in particular groups (such as disease refractory to other available treatments) can be detailed in the submissions made to NICE and considered by the committee during the appraisal. The NICE committee will consider the appropriateness of outcome measures used to capture HRQoL in this condition. The NICE committee can consider health-related quality of life impacts on carers as stated in the methods and process guide.

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		end-stage renal disease such as dialysis or transplant, and associated socio-economic costs such as the impact of further disease on ability to work, social life, and family life. Any other questions we feel able to comment on have been addressed in the appropriate sections above.	Taking into consideration the submissions and input from clinical experts, the committee will consider suitability for managed access, and benefits not included in the QALY.
	Otsuka Pharmaceuticals UK (comparator)	No further comments.	Noted, thank you
Additional comments on the draft scope	Kidney Research UK	We worked with the West London Renal and Transplant Centre, Hammersmith Hospital, Imperial College Healthcare NHS Trust to compile this consultation response	Noted, thank you
	Lupus UK	It is important to note that there is a forthcoming update, due to be published in early-to-mid-2025, of the British Society for Rheumatology (BSR) guidelines on the diagnosis and treatment of SLE, including lupus nephritis. These guidelines are likely to mirror the recently published updates to the EULAR guidelines (2023), which advocate more strongly for early combination therapy for lupus nephritis, more restricted use of corticosteroids, and not requiring two or more failures on immunosuppressive therapy before considering biologics. Therefore, if the current BSR guidelines are referenced in terms of current treatment paradigms for lupus nephritis, these updates should also be considered. <u>References</u> • EULAR (2023) updated guidelines:	Noted, thank you. No change needed. Any changes to existing guidelines can be considered during the appraisal.

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		○ Fanouriakis, A., Kostopoulou, M., Andersen, J., Aringer, M., Arnaud, L., Bae, S.C., Boletis, J., Bruce, I.N., Cervera, R., Doria, A. and Dörner, T., 2024. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. *Annals of the rheumatic diseases*, *83*(1), pp.15-29. • Current BSR guidelines ○ Gordon, C., Amissah-Arthur, M.B., Gayed, M., Brown, S., Bruce, I.N., D'Cruz, D., Empson, B., Griffiths, B., Jayne, D., Khamashta, M. and Lightstone, L., 2018. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. *Rheumatology*, *57*(1), pp.e1-e45. • Forthcoming update to BSR SLE guidelines: ○ Md Yusof, M.Y., Smith, E.M., Ainsworth, S., Armon, K., Beresford, M.W., Brown, M., Cherry, L., Edwards, C.J., Flora, K., Gilman, R. and Griffiths, B., 2023. Management and treatment of children, young people and adults with systemic lupus erythematosus: British Society for Rheumatology guideline scope. *Rheumatology Advances in Practice*, *7*(3), p.rkad093.	
	UK Kidney Association	In addition there is currently no suitably approved CD20 alternative to rituximab for patient who have a clear documented allergy to rituximab. No cross reactivity to obinutuzimab and greter theorectical and experienced efficacy Obinutuzumab to be evaluated for that purpose. Nationally, this is not an insignificant number as this has become acceptable practice at a number of trusts Yes used for both maintenance and induction. Experience at Imperial College Healthcare NHS Trust renal unit is that individual 1g doses provide decent remission, followed by a second dose several months later, based on clinical review and b-cell repletion. Prescribed in secondary care with routine follow-up in secondary care	Thank you for your comments. The benefits of obinutuzumab for people with an allergy to rituximab can be included in the submissions made to NICE and considered by the committee during the appraisal.